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Extending Pummerer Reaction Chemistry. Synthesis Studies in the Phakellin Alkaloid Area

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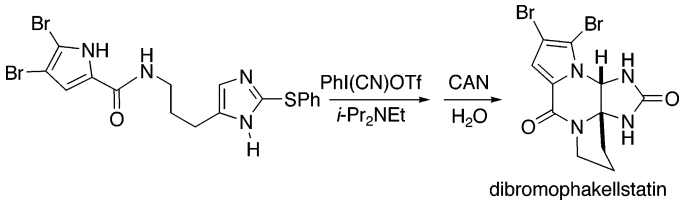

The syntheses of (±)-dibromophakellstatin and, from this species, (±)-dibromophakellin are described. Oxidative cyclization of a phenylthiolated dihydrooroidin derivative triggered by a Pummerer reaction constitutes the key step in this biomimetic approach to this family of marine alkaloids.

Introduction

The family of tetracyclic (and larger) sponge alkaloids presumably derived from oroidin (**11**) presents some significant challenges to organic synthesis from the standpoint of complexity, condensed functionality, and stereochemistry; see Figure 1.[1] Several different strategies have been pursued in synthesis projects targeting members of this class,[2] including approaches patterned on the bond formations implied in an oroidin-based biosynthesis.[3] Although the implementation of a biomimetic approach can take several forms (vide infra), the conceptualization of the problem as an oxidative cyclization of a dihydrooroidin derivative opened up the possibility of extending the recently developed Pummerer reaction-based indole oxidative cyclization transform[4] to imidazole substrates. The ultimate goal is to expand the utility of this methodology for achieving aromatic heterocycle oxidative cyclization. The full details of the development of this transform on an imidazole platform, in the context of (±)-dibromophakellstatin (**1**) synthesis, is described below.[2f] Subsequent conversion of this natural product to the related species (±)-dibromophakellin (**2a**) is documented as well.

(1) (a) For dibromophakellstatin, see: Pettit, G. R.; McNulty, J.; Herald, D. L.; Doubek, D. L.; Chapuis, J.-C.; Schmidt, J. M.; Tackett, L. P.; Boyd, M. R. *J. Nat. Prod.* **1997**, *60*, 180−183. (b) For dibromophakellin and monobromophakellin, see: Sharma, G.; Magdoff-Fairchild, B. *J. Org. Chem.* **1977**, *42*, 4118−4124. (c) For 7-*N*-methyldibromophakellin and 7-*N*-monobromophakellin, see: Gautschi, J. T.; Whitman, S.; Holman, T. R.; Crews, P. *J. Nat. Prod.* **2004**, *67*, 1256−1261. (d) For dibromoisophakellin, see: Fedoreev, S. A.; Utkina, N. K.; Ilíin, S. G.; Reshetnyak, M. V.; Maksimov, O. B. *Tetrahedron Lett.* **1986**, *27*, 3177−3180. (e) For monobromoisophakellin, see: Assmann, M.; Köck, M. *Z. Naturforsch.* **2002**, *57*, 153−156. (f) For 1-*N*-methyldibromoisophakellin, see: Assmann, M.; van Soest, R. W. M.; Köck, M. *J. Nat. Prod.* **2001**, *64*, 1354−1347. (g) For 12-chloro-11-hydroxydibromoisophakellin, see: Kitagawa, I.; Kobayashi, M.; Kitanaka, K.; Kido, M.; Kyogoku, Y. *Chem. Pharm. Bull.* **1983**, *31*, 2321−2328. (h) For palau'amine, monobromopalau'amine, and dibromopalau'amine, see: Kinnel, R. B.; Gehrken, H.-P.; Swali, R.; Skoropowski, G.; Scheuer, P. J. *J. Org. Chem.* **1998**, *63*, 3281−3286. (i) For konbu'acidin A, see: Koybashi, J.; Suzuki, M.; Tsuda, M. *Tetrahedron* **1997**, *53*, 15681−15684. (j) For styloguanidine, monobromostyloguanidine, and dibromostyloguanidine, see: Kato, T.; Shizuri, Y.; Izumida, H.; Yokoyama, A.; Endo, M. *Tetrahedron Lett.* **1995**, *36*, 2133−2136. (k) For structural/stereochemical revisions, see: Grube, A.; Köck, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2320−2324. (l) Buchanan, M. S.; Carroll, A. R.; Quinn, R. J. *Tetrahedron Lett.* **2007**, *48*, 4573−4574.

(2) For a general review, see: (a) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753−1783. For dibromophakellstatin, see: (b) Wiese, K. J.; Yakushijin, K.; Horne, D. A. *Tetrahedron Lett.* **2002**, *43*, 5135−5136. (c) Poullennec, K. G.; Romo, D. *J. Am. Chem. Soc.* **2003**, *125*, 6344−6345. (d) Chung, R.; Yu, E.; Incarvito, C. D.; Austin, D. J. *Org. Lett.* **2004**, *6*, 3881−3884. (e) Jacquot, D. E. N.; Zöllinger, M.; Lindel, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 2295−2298. (f) Feldman, K. S.; Skoumbourdis, A. P. *Org. Lett.* **2005**, *7*, 929−931. (g) Lu, J.; Tan, X.; Chen, C. *J. Am. Chem. Soc.* **2007**, *129*, 7768−7769. For dibromophakellin, see: (h) Büchi, G.; Foley, L. H. *J. Am. Chem. Soc.* **1982**, *104*, 1776−1777. (i) See ref 2b. (j) Travert, N.; Martin, M.-T.; Bourguet-Kondracki, M.-L.; Al Mourabit, A. *Tetrahedron Lett.* **2005**, *46*, 249−252. For palau'amine, see: (k) Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7159−7160. (l) Dilley, A. S.; Romo, D. *Org. Lett.* **2001**, *3*, 1535−1538. (m) Bélanger, G.; Hong, F.-T.; Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Org. Chem.* **2002**, *67*, 7880−7883. (n) Koenig, S. G.; Miller, S. M.; Leonard, K. A.; Löwe, R. S.; Chen, B. C.; Austin, D. J. *Org. Lett.* **2003**, *5*, 2203−2206. (o) Lovely, C. J.; Du, H.; He, Y.; Rasika Dias, H. V. *Org. Lett.* **2004**, *6*, 735−738. (p) Garrido-Hernandez, H.; Nakadai, M.; Vimolratana, M.; Li, Q.; Doundoulakis, T.; Harran, P. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 765−769.

(3) Al Mourabit, A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237−243.

(4) Feldman, K. S.; Boneva Vidulova, D.; Karatjas, A. G. *J. Org. Chem.* **2005**, *70*, 6429−6440.

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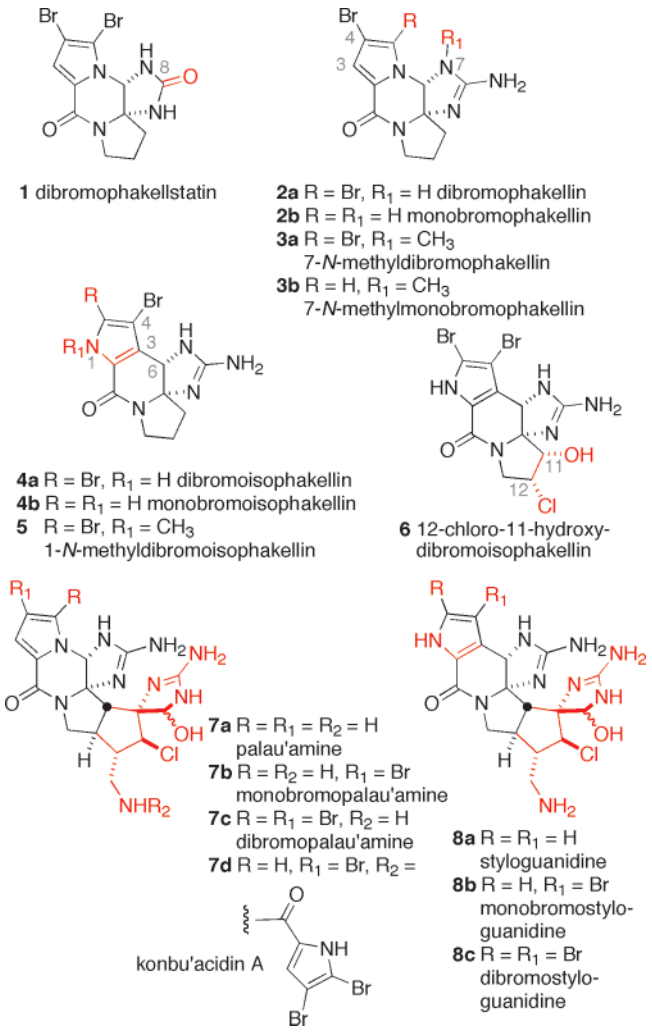
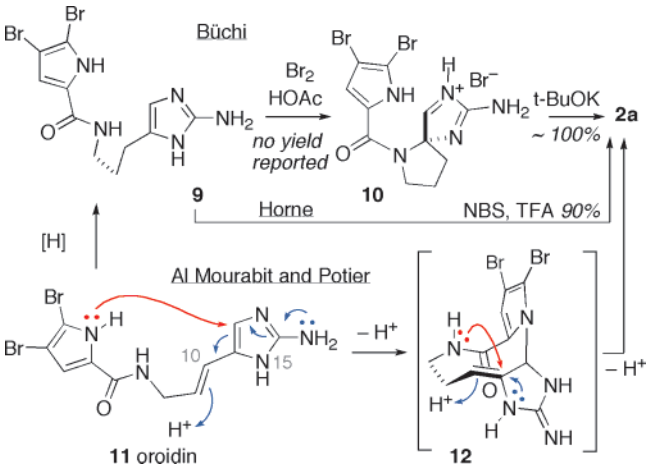


FIGURE 1. Members of the phakellin family of marine alkaloids.

The basic structural motif of the phakellin class of marine alkaloids is embodied in the inaugural member of this family, dibromophakellin (**2a**). Structural diversity is introduced by (a) variation of the number of bromines (e.g., **2b** and **4b**), (b) methylating a core nitrogen (**3a**, **3b**, and **5**), (c) incorporating higher oxidation (**6**), and finally, by (d) switching the N(1) → C(6) pyrrole attachment to a C(3) → C(6) connection (**4**, **5**, **6**, and **8**). The hexacyclic relatives pala'uamines (**7a**−**7c**), konbu'acidin A (**7d**), and styloguanidines (**8a**−**8c**) are formal oroidin dimers wherein one of the oroidin modules constitutes the phakellin (or isophakellin)-type tetracyclic core, and the second oroidin unit is appended to the pyrrolidine ring. As a bookkeeping mnemonic, the structural features of these species that distinguish them from the "parent" dibromophakellin are highlighted in red in Figure 1.

The recognition that the remarkable structural diversity of this collection of secondary metabolites all stems from the single simple precursor oroidin has fueled attempts to develop a biomimetic strategy for total synthesis of the representative member dibromophakellin (**2a**). The seminal work by Büchi (Scheme 1, **11** → **9** → **10** → **2a**) revealed that brominative activation of dihydrooroidin (**9**) is sufficient to promote the required oxidative cyclization and deliver the key spirocycle **10**.[2g] The ensuing base-mediated closure then delivered the intact tetracycle **2a**. Horne subsequently improved on this oxidative

SCHEME 1. Speculative Biosynthesis/Biomimetic Chemistry of Dibromophakellin



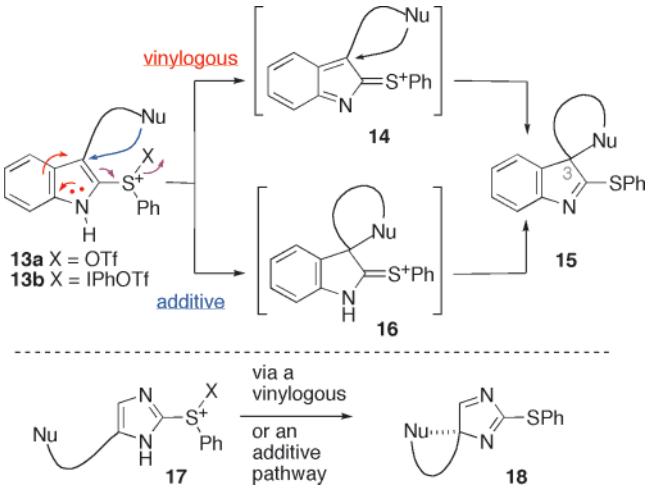
cyclization reaction by the expedient of using NBS in CF_3CO_2H to generate dibromophakellin in a remarkable 90% yield.[2b] As a counterpoint to this dihydrooroidin oxidative cyclization strategy, Al Mourabit and Potier favor a biosynthesis route for **2a** that features only proton-mediated isomerization of oroidin itself; see Scheme 1, **11** → **12** → **2a**.[3] A significant point of distinction between the two hypotheses lies in the regiochemistry of the first-formed N−C bond, as the Al Mourabit/Potier scheme proceeds through initial N(1)−C(6) bond formation to furnish a nine-membered lactam **12**. No experimental test of this hypothesis has appeared. The dihydrooroidin brominative cyclization approach has the appeal of simplicity and the benefit of successful implementation, but the extension of this experimental protocol (NBS in CF_3CO_2H) to some of the more complex and/or sensitive targets in Figure 1 raises concerns about compatibility/stability. From this perspective, the development of milder/more selective oxidative cyclization procedures may impact favorably on the larger question of total synthesis projects within the phakellin family.

The oxidative cyclization chemistry of aromatic heterocycles has been thoroughly explored with indole systems, but occasional problems of product overoxidation and/or unpredictable nucleophile addition regiochemistry have hampered the development of general protocols.[5] One approach to this transformation that avoids these issues by deliberate design involves the use of Pummerer chemistry to trigger the sequence; see Scheme 2, **13** → **15**. In this process, oxidation is confined to the reactive sulfur atom in the substrate, and the regiochemistry of nucleophilic addition (i.e., C(3)) is secured by the energy gain accompanying rearomatization from **14** to **15** in a vinylogous mechanism or, equivalently, by avoiding any disruption of the aryl ring in **13** via an additive mechanism.[6] A distinction between these two mechanistic paths has not yet been made. The extension of this chemistry to the imidazole nucleus is exemplified by the conversion of **17** into **18**, a spirocyclic species that bears some resemblance to the spirocyclic inter-

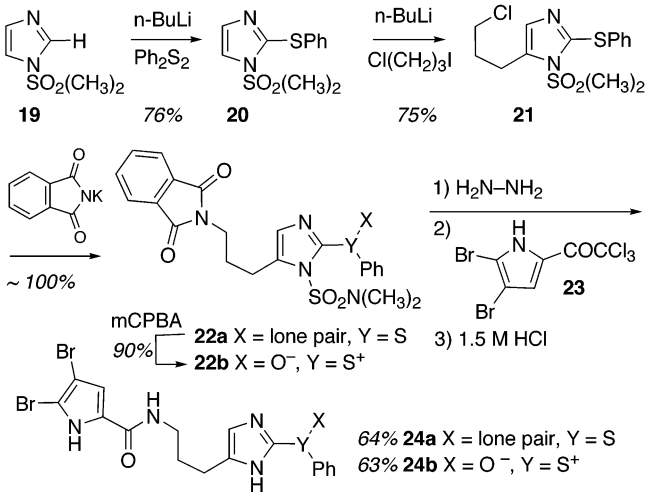
(5) (a) Somei, M.; Noguchi, K.; Yamagami, R.; Kawada, Y.; Yamada, K.; Yamada, F. *Heterocycles* **2000**, *53*, 7−10. (b) Wang, H.; Ganesan, A. *J. Org. Chem.* **2000**, *65*, 4685−4693. (c) Irikawa, H.; Mutoh, S.; Uehara, M.; Okumura, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3031−3033. (d) Güller, R.; Borschberg, H.-J. *Helv. Chim. Acta* **1993**, *76*, 847−862. (e) Braun, N. A.; Ousmer, M.; Bray, J. D.; Bouchu, D.; Peters, K.; Peters, E.-M.; Ciufolini, M. A. *J. Org. Chem.* **2000**, *65*, 4397−4408.

(6) Feldman, K. S. *Tetrahedron* **2006**, *62*, 5003−5034.

SCHEME 2. Pummerer-Chemistry-Initiated Oxidative Cyclization of Indoles and Imidazoles



SCHEME 3. Synthesis of a Thiophenyl Dihydrooroidin Oxidative Cyclization Precursor

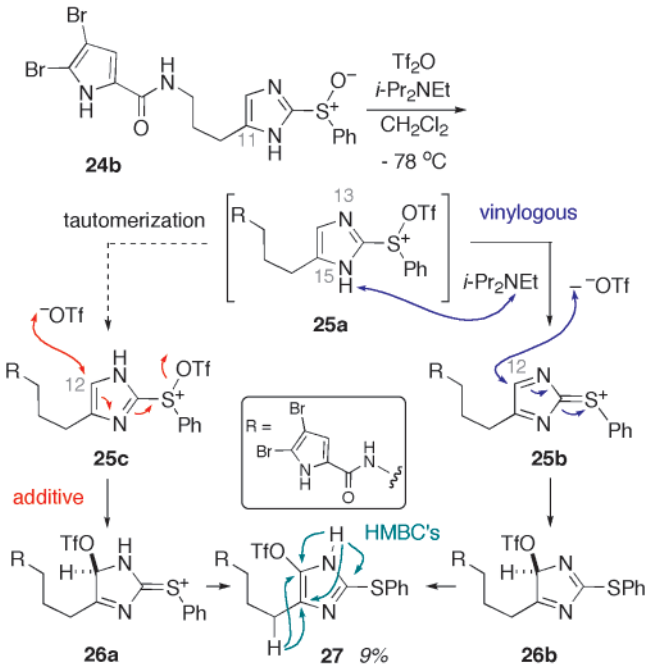


mediate **10** in the Büchi/Horne work. Thus, by appropriate choice of the nucleophile and tether, this reaction can be mapped into the dihydrooroidin-type oxidative cyclizations that already have documented utility in dibromophakellin synthesis. Successful demonstration of this proof-of-principle with the relatively well-explored dibromophakellin system can then lay the groundwork for future studies directed toward the more complex members of the phakellin family.

Results and Discussion

Exploration of the Pummerer-initiated oxidative cyclization chemistry of imidazoles required access to appropriate C(2)-sulfide and C(2)-sulfoxide imidazole substrates bearing a tethered nucleophile. The dihydrooroidin-based test substrates sulfide **24a** and sulfoxide **24b** were chosen as initial targets, given their relevance to the synthesis objectives in the phakellin area. Both species were prepared by straightforward imidazole lithiation chemistry as described by Vollinga,[7] Scheme 3. The differential kinetic acidity of the C(2) versus the C(5) proton of **19** could be exploited to permit sequential and regioselective

SCHEME 4. Pummerer-Mediated Oxidative Cyclization Attempt of an Imidazole 2-Sulfoxide



lithiation/thiolation (alkylation), leading to the C(2),C(5)-disubstituted intermediate **21**, with no evidence for regioisomer formation. Simple functional group manipulation of the imidazole chloride **21** furnished the requisite sulfide **24a**. The direct oxidation of **24a** into sulfoxide **24b** was capricious, and so, an alternative procedure featuring the earlier oxidation of the protected imidazole sulfide **22a** into the corresponding sulfoxide **22b** was pursued. In a manner identical to the **22a** → **24a** conversion, **22b** was processed into the requisite imidazole sulfoxide **24b**. The imidazole rings in **24** and other related structures in this paper are depicted as the 5-tautomer by analogy with the ^{1}H NMR-based assignment made for oroidin (**11**) by Lindel (HMBC correlation between ^{15}N(15) and H(10), oroidin numbering; see Scheme 1).[8] It is likely that the 4- and 5-imidazole tautomers interconvert under the (protic) oxidative cyclization conditions.

Initial oxidative cyclization experiments with the sulfoxides **24b** were anticipated to follow the successful indole sulfoxides chemistry, **13a** → **15**, but that expectation was not born out in practice. A limited survey of Pummerer initiation conditions, utilizing various activators (TFAA, Tf_2O) and bases (2,6-lutidine, *i*-Pr_2NEt), did not lead to the discovery of any protocols that favored formation of oxidative cyclization products of the type **18**. In almost all cases, starting sulfoxide **24b** was consumed without generation of any isolable/characterizable products. Eventually, a triflic anhydride-mediated procedure, which did furnish a small amount of a discrete reaction product **27** (Scheme 4), was identified. The spectroscopic data were consistent with the assigned structure **27** shown. Particularly, diagnostic information was provided by HMBC/HMQC spectra, with key correlations indicated on the structure (cf. Scheme 4). The conjecture that the imidazole N−H is adjacent to the triflate (imidazole-5-triflate) rather than adjacent to the alkyl chain (imidazole-4-triflate) is based upon lack of a three-bond correlation between this N−H and C(11) (phakellin numbering), and this tautomer assignment should be considered tentative.

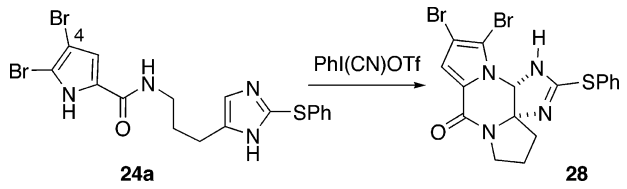
(7) Vollinga, R. C.; Menge, W. M. P. B.; Timmerman, H. *Recl. Trav. Pays-Bas* **1993**, *112*, 123−125.

(8) Köck, M.; Junker, J.; Lindel, T. *Org. Lett.* **1999**, *1*, 2041−2044.

Thus, in stark contrast to the previously studied indole series, a reactive, electrophilic intermediate **25** generated from classical Pummerer activation of sulfoxides **24b** did not trap the proximal nucleophilic nitrogen. Rather, the triflate counterion, in a rare display of nucleophilicity, apparently outcompeted this amide unit (attack at C(11), oroidin numbering) for the activated and electrophilic imidazole ring (attack at C(12)). Attack of triflate via an S_N1-like vinylogous Pummerer mechanism (**25a** → **25b** → **26b**) or the S_N2'-like additive alternative (**25a** → **25c** → **26a**) cannot be distinguished at this point. However, the additive channel does require a tautomerization of the imidazole ring prior to triflate attack. This point is significant because it raises the requirement that once N(15) is deprotonated (as per the vinylogous mechanism), the resultant anion must reprotonate at N(13) faster than it expels triflate for the additive mechanism to compete with the vinylogous alternative. Whatever the mechanistic subtleties, this result indicates that successful cyclization of an oroidin derivative into the phakellin skeleton via Pummerer methodology would require generating an electrophilic intermediate of the types **25a** or **25b** in the presence of a counterion even less nucleophilic than triflate.

In order to achieve this goal, attention was turned to a contemporary variant of Pummerer initiator, PhI(CN)OTf, as the discouraging results with sulfoxide **24b** and sulfonoylative initiators became apparent. This hypervalent iodine reagent was first introduced by Stang and Zhdankin as an effective iodonium transfer reagent useful for alkynyliodonium salt synthesis.[9] It appeared to be both a milder and a "softer" iodonium species than the more commonly used hypervalent reagents $PhI(OAc)_2$ or $PhI(OTFA)_2$, and as such, a preference for reaction with the "soft" sulfide's sulfur atom in **24a** over other electron-rich sites was anticipated. More importantly, previous use of this reagent in the context of alkynyliodonium salt/alkylidenecarbene chemistry did not reveal any instance of either triflate or cyanide acting as a nucleophile, even in the presence of highly reactive alkylidenecarbenes.[10] Initial trials with the other aforementioned hypervalent iodine reagents, which themselves were documented Pummerer triggers, did not lead to productive reaction. In contrast, the Stang reagent uniquely did promote tetracyclization of **24a** (Table 1) and, for the first time, did provide entry into the phakellin structural series. Optimization studies were pursued, and some trends can be discerned from the representative data presented in Table 1. The yield of tetracycle was not particularly sensitive to solvent, as yields in CH_2Cl_2 and toluene (−78 °C) or in CH_3CN and CF_3CH_2OH (0 °C) did not vary much. However, the incorporation of a small amount of methanol in CH_2Cl_2 did lead to consistently higher yields compared with pure CH_2Cl_2 (entry 9 vs 8). Temperature was a more important variable, as the product yield maximized at 25 °C, with notable yield dropoffs upon initiating the reaction sequence at temperatures ≥40 °C or dropping it to subzero regimes. Concentration appeared to be another contributor to success, as yields improved slightly at 5 mM compared with more concentrated solutions. A final critical component for achieving high-yielding tetracyclization was the portionwise addition of excess iodonium reagent as the reaction progressed. Decomposition of the PhI(CN)OTf appeared to compete with productive oxidation at sulfur, and continual replenishment of the oxidant proved essential to drive the process to completion. Product overoxidation did not present a problem (resubmission experiments). Neither the desbromo- nor the C(4) monobromo analogues of **24a** provided characterizable compounds upon exposure to Stang's reagent under optimized conditions. In both instances, the starting material was rapidly consumed, suggesting that both of the bromide substituents were necessary to protect the pyrrole ring from undesired oxidation by the iodonium reagent.

TABLE 1. Tetracyclization of 24a via Stang's Reagent, PhI(CN)OTf

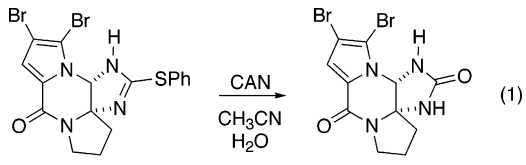


24a **28**

entry	solvent	conc (mM)	base	temp (°C)[a]	yield (%)[b]
1	toluene	10	2,6-lutidine	−78	6
2	CH_2Cl_2	10	2,6-lutidine	−78	7
3	CH_3CN	10	2,6-lutidine	−45	8
4	CF_3CH_2OH	100	2,6-lutidine	0	27
5	CH_3CN	10	2,6-lutidine	0	22
6	CH_2Cl_2	10	*i*-Pr_2NEt	5	27
7	CH_2Cl_2	10	*i*-Pr_2NEt	10	42
8	CH_2Cl_2	5	*i*-Pr_2NEt	25	48
9	**CH_2Cl_2/CH_3OH[c]**	**5**	***i*-Pr_2NEt**	**25**	**60−73**
10	CH_2Cl_2	5	*i*-Pr_2NEt	40	56
11	CH_2Cl_2/CH_3OH[c]	5	*i*-Pr_2NEt	40	48
12	CH_3CN	10	*i*-Pr_2NEt	45	40

[a] Temperature of mixing; in all cases, the reaction solution was then slowly brought to room temperature. [b] Yield of chromatographically pure product. [c] 1.5% by volume of CH_3OH added.

The stereochemistry of tetracycle formation was suggested by comparison of **28**'s spectral data with that recorded for dibromophakellstatin itself, and it was later confirmed by conversion of **28** into **1**, eq 1. This transformation formally amounted to no more than a hydrolysis of the thioamidine function within **28**, but it was accomplished with the greatest facility via the agency of the potent oxidant ceric ammonium nitrate (CAN). The thioamidine of **28** was immune to further oxidation by PhI(CN)OTf, a result readily rationalized by noting the resonance stabilization for sulfur's lone pair provided by the imine function in comparison to the lack of same in the starting thioimidazole in **24a**. However, the stronger oxidant CAN sufficed to generate a labile intermediate susceptible to hydrolysis by the H_2O present. Thus, the racemic natural product (±)-dibromophakellstatin (**1**) was available from imidazole dimethylsulfonamide (**19**) in eight steps, with an overall yield of 16%.



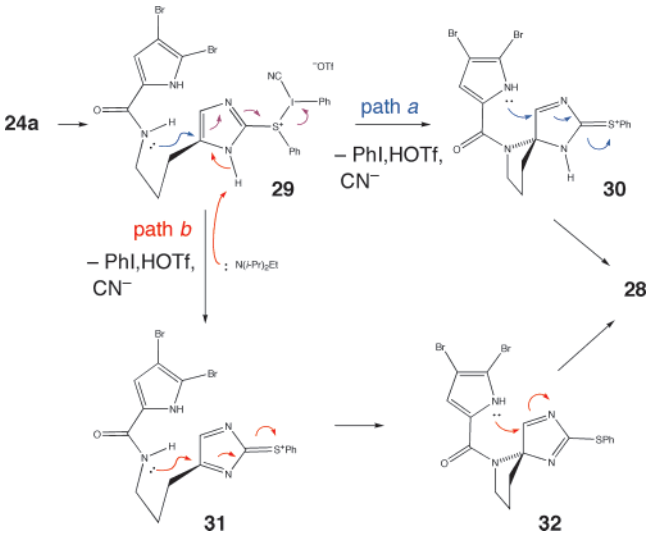
28 *80-93%* **1** (1)

The mechanistic course of this tetracyclization remains unsettled (Scheme 5). Within the working hypothesis that a

(9) Zhdankin, V. V.; Crittell, C. M.; Stang, P. J.; Zefirov, N. S. *Tetrahedron Lett.* **1990**, *31*, 4821−4824.

(10) (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523−2584. (b) Stang, P. J. *J. Org. Chem.* **2003**, *68*, 2997−3008. (c) Knorr, R. *Chem. Rev.* **2004**, *104*, 3795−3850.

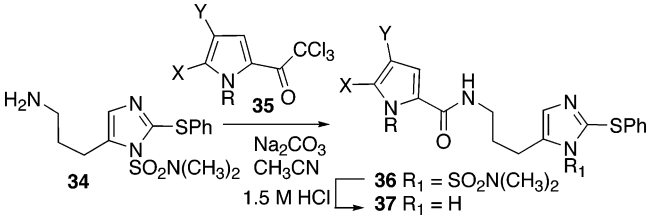
SCHEME 5. Mechanistic Speculation Governing the PhI(CN)OTf-Mediated Tetracyclization of 24a



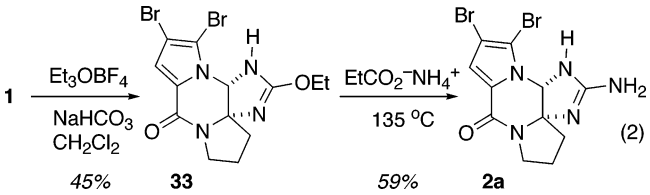
Pummerer transformation is operational, two distinct bond formation schemes can be envisioned, termed the additive Pummerer (path a) and the vinylogous Pummerer (path b). The latter sequence features elimination of the leaving group (**29** → **31**, − *H*-OTf) prior to N−C bond formation (**31** → **32**) and passes through the neutral imine electrophile **32** en route to the final N(1) → C(6) closure. The alternative additive pathway proceeds through direct S_N2'-like −OTf displacement within **29** prior to N−H proton loss, and this cyclization furnishes a presumably more electrophilic thionium ion-bearing imine **30** as a partner for the pyrrole's N(1). At present, there is no basis for distinguishing between these mechanistic options. In the related indole series, circumstantial evidence that is consistent with the additive sequence and not the vinylogous alternative has been recorded.

Much effort was expended in attempts to convert the thioamidine function of tetracycle **28** into the guanidine moiety of dibromophakellin (**2a**). Several different reagent protocols have been developed to facilitate this transformation, but none of these approaches proved effective with **28**. Thus, all procedures that featured either (a) direct displacement of the PhS unit of **28** with a nitrogen nucleophile (NH_3, $BnNH_2$, N_3^-)[11] or (b) oxidation of the sulfide to a sulfoxide or sulfone, followed by nitrogen nucleophile displacement,[12] led to one of two results, recovered **28** or complete destruction of the starting material without formation of any isolable compound(s). These failures led to a redirection of strategy that relied on much older chemistry for guanidine formation from ureas.[13a] Treatment of the synthesized natural product dibromophakellstatin (**1**) with Meerwein's salt furnished the 8-ethoxyamidine **33** as an isolable and completely stable (to alumina) white solid. Following a procedure developed by Jacobi,[13b] heating a mixture of **33** and ammonium propionate to 135 °C without solvent led to formation of the guanidine-containing product dibromophakellin (**2a**) in moderate yield. Pure product was isolated from the crude reaction mixture via Sephadex G-10 chromatography, and the spectral data for the synthesized **2a** (optical rotation excepted) matched those reported for the natural isolate in all respects (see Supporting Information). Attempts to apply this procedure to the thiophenyl substrate **28** did not meet with success; only decomposition of the starting material was observed. The success of these seemingly harsh reaction conditions on a demonstrably delicate substrate points to the possible utility of this transform in the synthesis of the more complex members of the oroidin family.

TABLE 2. Cyclization Substrates Explored in This Study



entry	R	X	Y	**36** (%)	**37** (%)
a	H	H	H	53	72
b	MOM	H	H	62	71
c	SEM	H	H	64	88
d	CH_3	H	H	82	76
e	H	H	Br	67	67
f	CH_3	H	Br	79	56
g	MOM	Br	Br	44	85
h	SEM	Br	Br	44	83
i	CH_3	Br	Br	80	63



Several other cyclization substrates, **37**, all bearing differing bromide and/or nitrogen substituents on the pyrrole ring, were examined in the Stang's reagent-mediated polycyclization cascade. These species were conveniently synthesized from primary amine **34** and the various pyrroles **35**, as indicated in Table 2. For example, an attempt was made to access the isophakellin skeleton (cf. **4a**/**4b**, **5**) by forcing pyrrole C(3) participation upon bond formation to the electrophilic carbon C(6). This redirection of the cascade sequence away from N(1) was probed with substrates **37g**−**37i**, all bearing a non-hydrogen substituent at the N(1) of the pyrrole. The substrates **37g**−**37i** feature pyrrole units with the full complement of bromides, but the monobromo species **37e** and **37f** were examined as well in the hopes that removing electron-withdrawing bromides might

(11) (a) Blythin, D. J.; Kaminski, J. J.; Domalski, M. S.; Spitler, J.; Solomon, D. M.; Conn, D. J.; Wong, S.; Verbiar, L. L.; Bober, L. A. *J. Med. Chem.* **1986**, *29*, 1099−1113. (b) Beljean-Leymarie, M.; Pays, M.; Richer, J. *Can. J. Chem.* **1983**, *61*, 2563−2566. (c) Flaherty, D.; Balse, P.; Li, K.; Moore, B. M.; Doughty, M. B. *Nucleosides Nucleotides* **1995**, *14*, 65−76. (d) Matsumoto, K.; Inoue, T.; Yoshioka, K.; Iio, H.; Tanaka, T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1553−1556. (e) Posteri, H.; Borghi, D.; Varasi, M. *Org. Lett.* **2005**, *7*, 5641−5644. (f) Reddick, R. E.; Kenyon, G. L. *J. Am. Chem. Soc.* **1987**, *109*, 4380−4387.

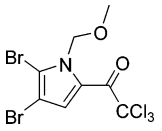
(12) (a) Meketa, M. L.; Weinreb, S. M. *Org. Lett.* **2006**, *8*, 1443−1446. (b) Chauviere, G.; Bouteille, B.; Enanga, B.; de Albuquerque, C.; Croft, S. L.; Dumas, M.; Perie, J. *J. Med. Chem.* **2003**, *46*, 427−440. (c) Bierer, D. E.; O'Connell, J. F.; Parquette, F. R.; Thompson, C. M.; Rapoport, H. *J. Org. Chem.* **1992**, *57*, 1390. (d) Zani, F.; Mazza, P.; Benvenuti, S.; Severi, F.; Malmusi, L.; Vampa, G.; Antolini, L. E. *J. Med. Chem.* **1995**, *30*, 729−740. (e) Ronne, E.; Grivas, S.; Olsson, K. *Acta Chem. Scand.* **1994**, *48*, 823−830.

(13) (a) Tanino, H.; Nakata, T.; Kaneka, T.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 2818−2819. (b) Jacobi, P. A.; Martinelli, M. J.; Slovenko, P. *J. Am. Chem. Soc.* **1984**, *106*, 5594−5595.

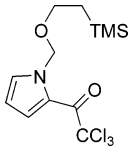
render the C(3) of the pyrrole ring correspondingly more nucleophilic. The end result, in all cases, was the same: no formation of tetracyclic material was evident. Uncharacterizable decomposition products accompanied all attempts at executing a Stang-reagent-mediated Pummerer oxidative cyclization with all of the sulfide substrates indicated in Table 2. Thus, it appears that the PhI(CN)OTf-mediated cyclization of thiophenylimidazole dihydrooriodin derivatives has a rather narrow scope but nevertheless works well for those species that bear tolerated substituents on the pyrrole ring.

In summary, the tetracyclic skeleton of the phakellins was readily prepared by Pummerer-mediated oxidative cyclization of a dihydrooriodin derivative featuring a phenylthio moiety at C(2) of the imidazole ring. Conversion of this cyclization product into (±)-dibromophakellstatin was straightforward (eight steps in total from protected imidazole **19**, 16% overall yield), and subsequent synthesis of (±)-dibromophakellin from dibromophakellstatin proceeded in two additional steps. Further attempts to fashion the isophakellin structure via oxidative cyclization of pyrrole-N-protected oroidin derivatives were not rewarded.

Experimental Section

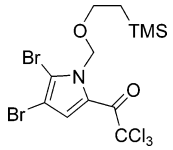


2,2,2-Trichloro-1-(4,5-dibromo-1-methoxymethyl-1H-pyrrol-2-yl)ethanone (35g). Following General Procedure D (Supporting Information), acyl pyrrole **23** (1.0 g, 2.7 mmol) in 10 mL of DMF was treated with NaH (0.119 g, 2.97 mmol) followed by MOM−Cl (0.250 mL, 3.24 mmol) to give 0.882 g (79%) of protected pyrrole **35g** as a colorless oil: IR (thin film) 1684 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.64 (s, 1H), 5.82 (s, 2H), 3.36 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 171.5, 126.0, 123.3, 119.4, 101.7, 95.1, 78.1, 56.4; LRMS (ESI) *m*/*z* (relative intensity) 411.8 (35% M + H^+); HRMS (ESI) *m*/*z* calcd for $[C_8H_7NO_2Br_2Cl_3]^+$, 411.7909; found, 411.7911.

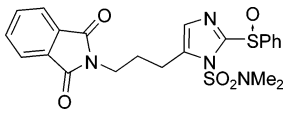


2,2,2-Trichloro-1-[1-(2-trimethylsilanylethoxymethyl)-1H-pyrrol-2-yl]ethanone (35c). Following General Procedure D (Supporting Information), acyl pyrrole **35a** (1.0 g, 4.7 mmol) in 10 mL of DMF was treated with NaH (0.207 g, 5.17 mmol) followed by SEM-Cl (0.917 mL, 5.18 mmol) to give 0.663 g (39%) of protected pyrrole **35c** as a yellow oil: IR (thin film) 1664 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.57 (dd, J = 4.3, 1.4 Hz, 1H), 7.22 (dd, J = 2.5, 1.8 Hz, 1H), 6.30 (dd, J = 4.3, 2.5 Hz, 1H), 5.71 (s, 2H), 3.57 (t, J = 8.3 Hz, 2H), 0.92 (t, J = 8.3 Hz, 2H), −0.03 (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 172.8, 132.4, 125.2, 121.5, 109.6, 96.2, 78.2, 66.5, 17.8, −1.5; LRMS (ESI) *m*/*z* (relative intensity) 364.0 (100% M + Na^+); HRMS (ESI) *m*/*z* calcd for $[C_{12}H_{18}NO_2Cl_3SiNa]^+$, 364.0070; found, 364.0065.

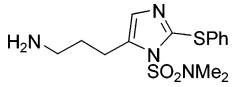
2,2,2-Trichloro-1-[4,5-dibromo-1-(2-trimethylsilanylethoxymethyl)-1H-pyrrol-2-yl]ethanone (35h). Following General Procedure D (Supporting Information), acyl pyrrole **23** (1.0 g, 2.7 mmol) in 10 mL of DMF was treated with NaH (0.119 g, 2.97 mmol) followed by SEM-Cl (0.478 mL, 3.34 mmol) to give 1.02 g (75%) of protected pyrrole **35h** as a yellow oil: IR (thin film)



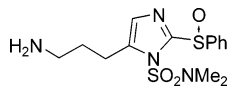
1684 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.56 (s, 1H), 5.81 (s, 2H), 3.55 (t, J = 8.3 Hz, 2H), 0.85 (t, J = 8.3 Hz, 2H), −0.09 (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 171.4, 125.8, 123.3, 119.3, 101.5, 95.2, 76.0, 66.4, 17.7, −1.4; LRMS (ESI) *m*/*z* (relative intensity) 514.9 (85% M + NH_4^+); HRMS (ESI) *m*/*z* calcd for $[C_{12}H_{20}N_2Br_2O_2Cl_3Si]^+$, 514.8726; found, 514.8737.



2-Benzenesulfinyl-5-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-propyl]imidazole-1-sulfonic Acid Dimethylamide (22b). A stirring solution of phthalimidosulfide **22a** (21.8 g, 46.3 mmol) in 250 mL of CH_2Cl_2 was cooled to 0 °C and treated with *m*CPBA (8.00 g, 46.3 mmol). After 60 min, the reaction solution was warmed to room temperature and poured into aqueous $NaHCO_3$ (200 mL). The resulting solution was partitioned between CH_2Cl_2 and H_2O, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The organic fractions were combined, dried with Na_2SO_4, and concentrated to give a yellow oil. Purification of this oil by flash column chromatography (gradient 50−90% EtOAc/hexanes) afforded 22.8 g (98%) of phthalimidosulfoxide **22b** as a white solid: mp 45−47 °C; IR (thin film) 1713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74−7.67 (m, 4H), 7.62−7.57 (m, 2H), 7.38−7.32 (m, 3H), 6.94 (s, 1H), 3.65 (t, J = 6.8 Hz, 2H), 2.80 (s, 6H), 2.76−2.57 (m, 2H), 1.95 (quint, J = 7.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 150.7, 142.8, 135.1, 133.7, 131.4, 131.3, 128.7, 128.5, 125.9, 122.8, 37.5, 36.8, 26.4, 22.6; LRMS (ESI) *m*/*z* (relative intensity) 487.1 (100% M + H^+); HRMS (ESI) *m*/*z* calcd for $[C_{22}H_{23}N_4O_5S_2]^+$, 487.1112; found, 487.1110.

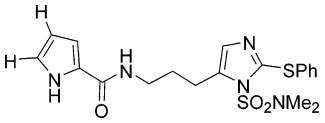


5-(3-Aminopropyl)-2-phenylsulfanylimidazole-1-sulfonic Acid Dimethylamide (34). Following General Procedure A (Supporting Information), phthalimidosulfide **22a** (4.28 g, 9.09 mmol) in 90 mL of EtOH was heated to reflux and treated with hydrazine (5.7 mL, 180 mmol) to give 2.67 g (86%) of aminosulfide **34** as a white solid: mp 42−43 °C; IR (thin film) 3364 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50−7.47 (m, 2H), 7.39−7.34 (m, 3H), 6.65 (app d, J = 1.0 Hz, 1H), 2.99 (s, 6H), 2.80 (t, J = 7.6 Hz, 4H), 1.79 (quint, J = 7.5 Hz, 2H), 1.27 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 135.8, 132.5, 131.0, 129.0, 128.3, 127.7, 41.4, 38.1, 32.0, 23.8; LRMS (ESI) *m*/*z* (relative intensity) 341.1 (100% M + H^+); HRMS (ESI) *m*/*z* calcd for $[C_{14}H_{21}N_4O_2S_2]^+$, 341.1106; found, 341.1103.

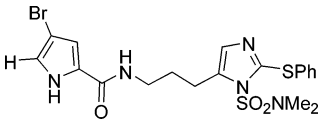


5-(3-Aminopropyl)-2-benzenesulfinylimidazole-1-sulfonic Acid Dimethylamide. Following General Procedure A (Supporting Information), phthalimidosulfoxide **22b** (22.0 g, 45.2 mmol) in 500 mL of EtOH was heated to reflux and treated with hydrazine (31.2 mL, 937 mmol) to give 11.4 g (71%) of the aminosulfoxide product as an unstable colorless oil: IR (thin film) 3442 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80−7.74 (m, 2H), 7.48−7.33 (m, 3H), 6.91 (s, 1H), 2.87 (s, 6H), 2.67 (m, 4H), 1.71 (quint, J = 7.4 Hz, 2H),

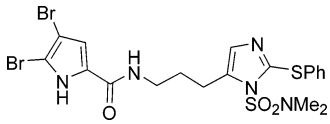
1.51 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 142.9, 136.3, 131.5, 128.9, 128.7, 126.0, 41.1, 37.8, 31.2, 22.6; LRMS (ESI) *m*/*z* (relative intensity) 357.1 (100% M + H$^+$); HRMS (ESI) *m*/*z* calcd for $[C_{14}H_{21}N_4O_3S_2]^+$, 357.1055; found, 357.1071.



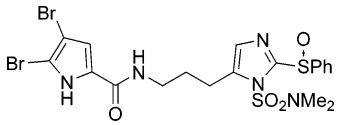
1H-Pyrrole-2-carboxylic Acid [3-(3-Dimethylsulfamoyl-2-phenylsulfanyl-3H-imidazol-4-yl)propyl]amide (36a). Following General Procedure B (Supporting Information), amine **34** (0.150 g, 0.441 mmol) in 5 mL of MeCN was treated consecutively with Na_2CO_3 (0.046 g, 0.43 mmol) followed by acyl pyrrole **35a** (0.094 g, 0.44 mmol) to give 0.102 g (53%) of amidosulfide **36a** as a colorless oil: IR (thin film) 3250, 1627 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.53 (br s, 1H), 7.61−7.48 (m, 2H), 7.41−7.34 (m, 3H), 6.90 (dt, J = 2.6, 1.2 Hz, 1H), 6.77 (s, 1H), 6.58 (ddd, J = 3.6, 2.4, 1.5 Hz, 1H), 6.22 (app dt, J = 3.6, 2.6 Hz, 1H), 6.19 (t, J = 5.6 Hz, 1H), 3.48 (q, J = 6.3 Hz, 2H), 2.97 (s, 6H), 2.82 (t, J = 7.5 Hz, 2H), 1.92 (quint, J = 6.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 143.7, 135.3, 132.7, 130.8, 129.1, 128.5, 128.0, 125.7, 121.6, 109.33, 109.26, 38.6, 38.1, 28.7, 23.8; LRMS (ESI) *m*/*z* (relative intensity) 434.1(100% M + H$^+$); HRMS (ESI) *m*/*z* calcd for $[C_{19}H_{24}N_5O_3S_2]^+$, 434.1321; found, 434.1333.



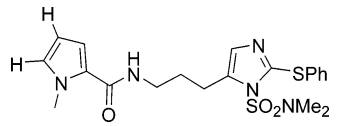
4-Bromo-1H-pyrrole-2-carboxylic Acid [3-(3-Dimethylsulfamoyl-2-phenylsulfanyl-3H-imidazol-4-yl)propyl]amide (36e). Following General Procedure B (Supporting Information), amine **34** (0.150 g, 0.441 mmol) in 5 mL of MeCN was treated consecutively with Na_2CO_3 (0.046 g, 0.43 mmol) followed by acyl pyrrole **35e** (0.128 g, 0.441 mmol) to give 0.174 g (67%) of amidosulfide **36e** as a white solid: mp 146−148 °C; IR (thin film) 3215, 1629 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (br s, 1H), 7.50−7.47 (m, 2H), 7.38−7.34 (m, 3H), 6.88 (dd, J = 2.2, 1.1 Hz, 1H), 6.77 (s, 1H), 6.56 (dd, J = 2.0, 1.1 Hz, 1H), 6.17 (t, J = 5.1 Hz, 1H), 3.45 (q, J = 6.5 Hz, 2H), 2.98 (s, 6H), 2.85 (t, J = 7.2 Hz, 2H), 1.91 (quint, J = 6.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4, 144.1, 135.3, 133.1, 130.7, 129.30, 128.8, 128.3, 126.1, 121.4, 111.0, 96.9, 38.8, 38.4, 29.0, 23.9; LRMS (ESI) *m*/*z* (relative intensity) 512.1 (100% M + H$^+$); HRMS (ESI) *m*/*z* calcd for $[C_{19}H_{23}BrN_5O_3S_2]^+$, 512.0426; found, 512.0443.



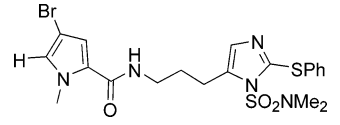
4,5-Dibromo-1H-pyrrole-2-carboxylic Acid [3-(3-Dimethylsulfamoyl-2-phenylsulfanyl-3H-imidazol-4-yl)propyl]amide. Following General Procedure B (Supporting Information), amine **34** (0.203 g, 0.548 mmol) in 5 mL of MeCN was treated consecutively with Na_2CO_3 (0.058 g, 0.55 mmol) followed by acyl pyrrole **23** (0.187 g, 0.548 mmol) to give 0.282 g (87%) of amidosulfide product as a white solid: mp 123−124 °C; IR (thin film) 3117, 1643 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (br s, 1H), 7.46−7.44 (m, 2H), 7.42−7.35 (m, 3H), 6.87 (s, 1H), 6.53 (s, 1H), 3.23 (q, J = 6.5 Hz, 2H), 2.93 (s, 6H), 2.72 (t, J = 7.4 Hz, 2H), 1.75 (quint, J = 7.1 Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 161.7, 142.2, 135.6, 132.6, 131.3, 130.9, 129.2, 128.4, 127.7, 112.2, 108.5, 94.7, 37.9, 37.8, 28.0, 23.5; LRMS (ESI) *m*/*z* (relative intensity) 589.9 (100% M + H$^+$); HRMS (ESI) *m*/*z* calcd for $[C_{19}H_{22}Br_2N_5O_3S_2]^+$, 589.9531; found, 589.9510.



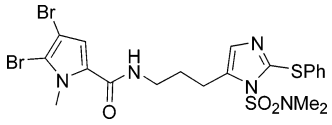
4,5-Dibromo-1H-pyrrole-2-carboxylic Acid [3-(2-Benzenesulfinyl-3-dimethylsulfamoyl-3H-imidazol-4-yl)propyl]amide. Following General Procedure B (Supporting Information), 5-(3-aminopropyl)-2-benzenesulfinylimidazole-1-sulfonic acid dimethylamide (2.49 g, 6.98 mmol) in 20 mL of MeCN was treated consecutively with Na_2CO_3 (0.658 g, 6.98 mmol) followed by acyl pyrrole **23** (2.59 g, 6.98 mmol) to give 1.95 g (46%) of amidosulfoxide product as an off-white solid: mp 172−174 °C; IR (thin film) 3331, 1634 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (t, J = 5.5 Hz, 1H), 7.74−7.72 (m, 2H), 7.56−7.54 (m, 3H), 7.13 (s, 1H), 6.83 (s, 1H), 3.29 (q, J = 6.2 Hz, 2H), 2.91 (s, 6H), 2.74 (t, J = 7.4 Hz, 2H), 1.84 (quint, J = 6.5 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.0, 150.3, 143.0, 136.1, 131.1, 129.3, 128.7, 128.1, 125.6, 112.2, 105.7, 96.1, 37.7, 37.3, 27.4, 22.2; LRMS (ESI) *m*/*z* (relative intensity) 605.9 (100% M + H$^+$); HRMS (ESI) *m*/*z* calcd for $[C_{19}H_{22}Br_2N_5O_4S_2]^+$, 605.9480; found, 605.9593.



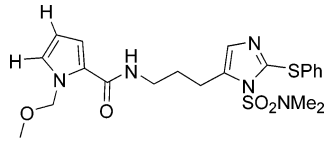
1-Methyl-1H-pyrrole-2-carboxylic Acid [3-(3-Dimethylsulfamoyl-2-phenylsulfanyl-3H-imidazol-4-yl)propyl]amide (36d). Following General Procedure B (Supporting Information), amine **34** (0.150 g, 0.441 mmol) in 5 mL of MeCN was treated consecutively with Na_2CO_3 (0.046 g, 0.43 mmol) followed by acyl pyrrole **35d** (0.100 g, 0.441 mmol) to give 0.162 g (82%) of amidosulfide **36d** as a colorless oil: IR (thin film) 3326, 1634 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47−7.42 (m, 2H), 7.35−7.32 (m, 3H), 6.73 (s, 1H), 6.66 (app t, J = 1.6 Hz, 1H), 6.54 (dd, J = 3.9, 1.6 Hz, 1H), 6.36 (t, J = 5.6 Hz, 1H), 6.02 (dt, J = 2.6, 1.2 Hz, 1H), 3.89 (s, 3H), 3.63 (q, J = 6.6 Hz, 2H), 2.93 (s, 6H), 2.82 (t, J = 7.6 Hz, 2H), 1.87 (quint, J = 6.9 Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 161.9, 143.4, 135.3, 132.6, 130.8, 129.0, 128.4, 127.9, 127.5, 125.4, 111.3, 106.9, 38.3, 38.0, 36.4, 28.7, 23.8; LRMS (ESI) *m*/*z* (relative intensity) 448.1 (100% M + H$^+$); HRMS (ESI) *m*/*z* calcd for $[C_{20}H_{26}N_5O_3S_2]^+$, 448.1477; found, 448.1475.



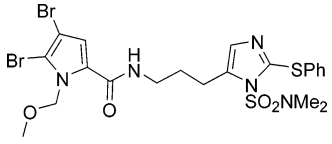
4-Bromo-1-methyl-1H-pyrrole-2-carboxylic Acid [3-(3-Dimethylsulfamoyl-2-phenylsulfanyl-3H-imidazol-4-yl)propyl]amide (36f). Following General Procedure B (Supporting Information), amine **34** (0.150 g, 0.441 mmol) in 5 mL of MeCN was treated consecutively with Na_2CO_3 (0.046 g, 0.43 mmol) followed by acyl pyrrole **35f** (0.135 g, 0.441 mmol) to give 0.184 g (79%) of amidosulfide **36f** as a white solid: mp 144−145 °C; IR (thin film) 3307, 1644 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.45 (m, 2H), 7.38−7.32 (m, 3H), 6.74 (s, 1H), 6.66 (d, J = 1.8 Hz, 1H), 6.52 (d, J = 1.8 Hz, 1H), 6.25 (t, J = 5.5 Hz, 1H), 3.87 (s, 3H), 3.38 (q, J = 6.6 Hz, 2H), 2.98 (s, 6H), 2.83 (t, J = 7.4 Hz, 2H), 1.88 (quint, J = 6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 143.7, 135.3, 132.8, 130.8, 129.2, 128.6, 128.1, 127.0, 126.2, 113.2, 94.2, 38.6, 38.3, 36.7, 28.8, 24.0; LRMS (ESI) *m*/*z* (relative intensity) 526.0 (100% M + H$^+$); HRMS (ESI) *m*/*z* calcd for $[C_{20}H_{25}BrN_5O_3S_2]^+$, 526.0589; found, 526.0585.



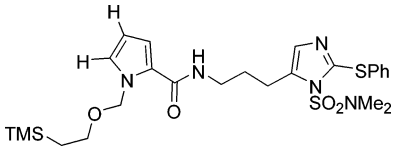
4,5-Dibromo-1-methyl-1H-pyrrole-2-carboxylic Acid [3-(3-Dimethylsulfamoyl-2-phenylsulfanyl-3H-imidazol-4-yl)propyl]-amide (36i). Following General Procedure B (Supporting Information), amine **34** (0.150 g, 0.441 mmol) in 5 mL of MeCN was treated consecutively with Na_2CO_3 (0.046 g, 0.43 mmol) followed by acyl pyrrole **35i** (0.170 g, 0.441 mmol) to give 0.214 g (80%) of amidosulfide **36i** as a white solid: mp 68−70 °C; IR (thin film) 3317, 1644 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49−7.46 (m, 2H), 7.37−7.35 (m, 3H), 6.76 (s, 1H), 6.23 (s, 1H), 6.14 (t, J = 6.6 Hz, 1H), 3.93 (s, 3H), 3.40 (q, J = 6.5 Hz, 2H), 2.99 (s, 6H), 2.82 (t, J = 7.5 Hz, 2H), 1.91 (quint, J = 6.8 Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 160.5, 144.0, 135.3, 133.0, 130.8, 129.30, 128.7, 128.3, 127.6, 111.5, 109.5, 97.8, 38.7, 38.4, 35.6, 29.0, 24.0; LRMS (ESI) *m*/*z* (relative intensity) 604.0 (100% M + H^+); HRMS (ESI) *m*/*z* calcd for $[C_{20}H_{23}Br_2N_5O_3S_2]^+$, 603.9687; found, 603.9691.



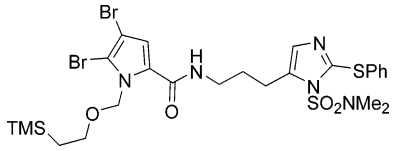
1-Methoxymethyl-1H-pyrrole-2-carboxylic Acid [3-(3-Dimethylsulfamoyl-2-phenylsulfanyl-3H-imidazol-4-yl)propyl]amide (36b). Following General Procedure B (Supporting Information), amine **34** (0.226 g, 0.881 mmol) in 5 mL of MeCN was treated consecutively with Na_2CO_3 (0.094 g, 0.88 mmol) followed by acyl pyrrole **35b** (0.300 g, 0.881 mmol) to give 0.260 g (62%) of amidosulfide **36b** as a colorless oil: IR (thin film) 3331, 1641 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.49−7.46 (m, 2H), 7.39−7.33 (m, 3H), 6.90 (dd, J = 2.9, 1.8 Hz, 1H), 6.76 (s, 1H), 6.67 (dd, J = 4.0, 1.8 Hz, 1H), 6.44 (t, J = 5.8 Hz, 1H), 6.14 (dd, J = 3.6, 2.5 Hz, 1H), 5.61 (s, 2H), 3.43 (q, J = 6.8 Hz, 2H), 3.30 (s, 3H), 2.97 (s, 6H), 2.82 (t, J = 6.8 Hz, 2H), 1.91 (quint, J = 6.5 Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 161.6, 143.7, 135.3, 132.8, 130.8, 129.2, 128.6, 128.1, 126.8, 126.2, 113.5, 108.1, 78.5, 55.9, 38.6, 38.3, 28.8, 24.0; LRMS (ESI) *m*/*z* (relative intensity) 478.1 (100% M + H^+); HRMS (ESI) *m*/*z* calcd for $[C_{21}H_{28}N_5O_4S_2]^+$, 478.1583; found, 478.1584.



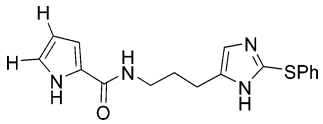
4,5-Dibromo-1-methoxymethyl-1H-pyrrole-2-carboxylic Acid [3-(3-Dimethylsulfamoyl-2-phenylsulfanyl-3H-imidazol-4-yl)propyl]amide (36g). Following General Procedure B (Supporting Information), amine **34** (0.300 g, 0.881 mmol) in 5 mL of MeCN was treated consecutively with Na_2CO_3 (0.093 g, 0.97 mmol) followed by acyl pyrrole **35g** (0.402 g, 0.969 mmol) to give 0.246 g (44%) of amidosulfide **36g** as a white oil: IR (thin film) 3310, 1651 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.48−7.46 (m, 2H), 7.39−7.33 (m, 3H), 6.75 (s, 1H), 6.74 (s, 1H), 6.54 (t, J = 5.0 Hz, 1H), 5.74 (s, 2H), 3.41 (q, J = 6.5 Hz, 2H), 3.35 (s, 3H), 2.98 (s, 6H), 2.81 (t, J = 7.6 Hz, 2H), 1.89 (quint, J = 6.8 Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 160.0, 144.0, 135.3, 133.0, 130.8, 129.4, 128.8, 128.7, 128.4, 115.6, 111.0, 100.6, 77.8, 56.3, 38.9, 38.4, 29.0, 24.1; LRMS (ESI) *m*/*z* (relative intensity) 634.0 (100% M + H^+); HRMS (ESI) *m*/*z* calcd for $[C_{21}H_{26}Br_2N_5O_4S_2]^+$, 633.9814; found, 633.9805.



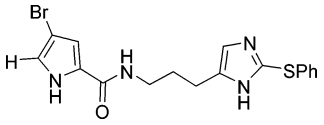
1-(2-Trimethylsilanylethoxymethyl)-1H-pyrrole-2-carboxylic Acid [3-(3-Dimethylsulfamoyl-2-phenylsulfanyl-3H-imidazol-4-yl)propyl]amide (36c). Following General Procedure B (Supporting Information), amine **34** (0.317 g, 0.923 mmol) in 5 mL of MeCN was treated consecutively with Na_2CO_3 (0.098 g, 0.92 mmol) followed by acyl pyrrole **35c** (0.314 g, 0.923 mmol) to give 0.334 g (64%) of amidosulfide **36c** as a colorless oil: IR (thin film) 3331, 1641 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.49−7.46 (m, 2H), 7.39−7.33 (m, 3H), 6.89 (dd, J = 2.5, 1.4 Hz, 1H), 6.76 (s, 1H), 6.67 (dd, J = 3.6, 1.4 Hz, 1H), 6.55 (t, J = 7.6, 1H), 6.13 (dd, J = 4.0, 2.8 Hz, 1H), 5.63 (s, 2H), 3.54 (t, J = 8.3 Hz, 2H), 3.44 (q, J = 6.5 Hz, 2H), 2.97 (s, 6H), 2.83 (t, J = 7.2 Hz, 2H), 1.91 (quint, J = 6.8 Hz, 2H), 0.90 (t, J = 8.3 Hz, 2H), −0.04 (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 161.6, 143.6, 135.3, 132.8, 130.9, 129.2, 128.6, 128.1, 126.5, 126.4, 113.6, 108.1, 76.6, 65.8, 38.6, 38.2, 28.8, 24.0, 17.6, −1.57; LRMS (ESI) *m*/*z* (relative intensity) 564.2 (100% M + H^+); HRMS (ESI) *m*/*z* calcd for $[C_{25}H_{38}N_5O_4S_2Si]^+$, 564.2143; found, 564.2141.



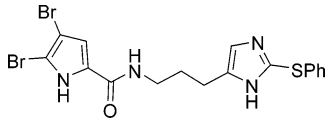
4,5-Dibromo-1-(2-trimethylsilanylethoxymethyl)-1H-pyrrole-2-carboxylic Acid [3-(3-Dimethylsulfamoyl-2-phenylsulfanyl-3H-imidazol-4-yl)propyl]amide (36h). Following General Procedure B (Supporting Information), amine **34** (0.300 g, 0.881 mmol) in 5 mL of MeCN was treated consecutively with Na_2CO_3 (0.093 g, 0.97 mmol) followed by acyl pyrrole **35h** (0.485 g, 0.969 mmol) to give 0.282 g (44%) of amidosulfide **36h** as a colorless oil: IR (thin film) 3326, 1651 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.50−7.47 (m, 2H), 7.39−7.34 (m, 3H), 6.76 (s, 2H), 6.60 (t, J = 5.4 Hz, 1H), 5.74 (s, 2H), 3.61 (dt, J = 8.3, 2.9 Hz, 2H), 3.41 (q, J = 6.5 Hz, 2H), 2.99 (s, 6H), 2.83 (t, J = 7.2 Hz, 2H), 1.91 (quint, J = 6.8 Hz, 2H), 0.91 (dt, J = 8.3, 2.9 Hz, 2H), −0.03 (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 160.1, 143.9, 135.3, 132.9, 130.8, 129.3, 128.9, 128.8, 128.3, 115.8, 110.7, 99.9, 75.1, 66.2, 39.0, 38.4, 28.9, 24.1, 17.8, −1.46; LRMS (ESI) *m*/*z* (relative intensity) 720.1 (100% M + H^+); HRMS (ESI) *m*/*z* calcd for $[C_{25}H_{36}Br_2N_5O_4S_2Si]^+$, 720.0345; found, 720.0362.



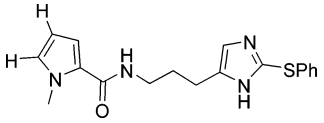
1H-Pyrrole-2-carboxylic Acid [3-(2-Phenylsulfanyl-3H-imidazol-4-yl)propyl]amide (37a). Following General Procedure C (Supporting Information), amide **36a** (0.084 g, 0.19 mmol) in 3 mL of THF was heated to reflux and treated with 0.516 mL of a 1.5 M HCl solution to give 0.054 g (85%) of the deprotection product **37a** as a colorless oil: IR (thin film) 3212, 1613 cm^{-1}; ^1H NMR (400 MHz, d_4-MeOH) δ 7.26−7.22 (m, 2H), 7.18−7.14 (m, 3H), 6.94 (s, 1H), 6.88 (dd, J = 2.2, 1.1 Hz, 1H), 6.76 (dd, J = 3.6, 1.0 Hz, 1H), 6.14 (app t, J = 2.5 Hz, 1H), 3.35 (t, J = 6.8 Hz, 2H), 2.64 (t, J = 7.6 Hz, 2H), 1.81 (quint, J = 7.1 Hz, 2H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 162.3, 137.3, 136.8, 132.4, 131.2, 130.5, 130.2, 126.3, 122.9, 119.5, 111.7, 110.0, 38.6, 28.7, 22.6; LRMS (ESI) *m*/*z* (relative intensity) 327.1 (100% M + H^+); HRMS (ESI) *m*/*z* calcd for $[C_{17}H_{19}N_4OS]^+$, 327.1280; found, 327.1284.



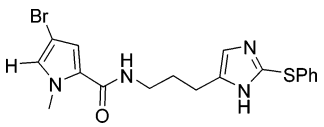
4-Bromo-1H-pyrrole-2-carboxylic Acid [3-(2-Phenylsulfanyl-3H-imidazol-4-yl)propyl]amide (37e). Following General Procedure C (Supporting Information), amide **36e** (0.161 g, 0.314 mmol) in 3 mL of THF was heated to reflux and treated with 0.837 mL of a 1.5 M HCl solution to give 0.085 g (67%) of the deprotection product **37e** as a colorless oil: IR (thin film) 3183, 1622 cm^{-1}; ^1H NMR (300 MHz, d_4-MeOH) δ 7.26−7.22 (m, 2H), 7.18−7.14 (m, 3H), 6.95 (br s, 1H), 6.88 (d, J = 1.5 Hz, 1H), 6.77 (d, J = 1.5 Hz, 1H), 3.33 (t, J = 6.9 Hz, 2H), 2.63 (t, J = 7.5 Hz, 2H), 1.85 (quint, J = 7.0 Hz, 2H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 161.0, 137.1, 137.0, 132.4, 131.1, 130.4, 130.0, 127.1, 122.5, 119.4, 112.8, 96.2, 38.6, 28.5, 22.6; LRMS (ESI) m/z (relative intensity) 405.0 (100% M + H^+); HRMS (ESI) m/z calcd for $[C_{17}H_{18}BrN_4OS]^+$, 405.0388; found, 405.0359.



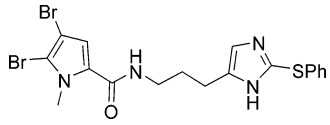
4,5-Dibromo-1H-pyrrole-2-carboxylic Acid [3-(2-Phenylsulfanyl-3H-imidazol-4-yl)propyl]amide (24a). Following General Procedure C (Supporting Information), 4,5-dibromo-1H-pyrrole-2-carboxylic acid [3-(3-dimethylsulfamoyl-2-phenylsulfanyl-3H-imidazol-4-yl)propyl]amide (0.310 g, 0.524 mmol) in 2 mL of THF was heated to reflux and treated with 2.80 mL of a 1.5 M HCl solution to give 0.240 g (95%) of the deprotection product **24a** as a white solid previously described by Feldman and Skoumbourdis.[2f]



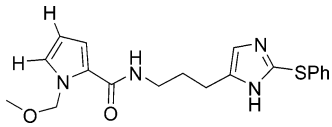
1-Methyl-1H-pyrrole-2-carboxylic Acid [3-(2-Phenylsulfanyl-3H-imidazol-4-yl)propyl]amide (37d). Following General Procedure C (Supporting Information), amide **36d** (0.125 g, 0.279 mmol) in 3 mL of THF was heated to reflux and treated with 0.774 mL of a 1.5 M HCl solution to give 0.072 g (76%) of the deprotection product **37d** as a colorless oil: IR (thin film) 3059, 1631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15−7.09 (m, 5H), 6.95 (br s, 1H), 6.78 (s, 1H), 6.73 (br t, J = 6.0 Hz, 1H), 6.65 (app t, J = 1.8 Hz, 1H), 6.57 (dd, J = 3.9, 1.6 Hz, 1H), 6.00 (dd, J = 3.9, 2.6 Hz, 1H), 3.83 (s, 3H), 3.33 (t, J = 6.3 Hz, 2H), 2.59 (t, J = 6.8 Hz, 2H), 1.73 (quint, J = 6.6 Hz, 2H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 163.6, 137.53, 137.46, 132.9, 131.5, 130.9, 130.1, 129.7, 126.0, 119.5, 114.1, 108.4, 37.30, 37.26, 28.8, 22.9; LRMS (ESI) m/z (relative intensity) 341.1 (100% M + H^+); HRMS (ESI) m/z calcd for $[C_{18}H_{21}N_4OS]^+$, 341.1436; found, 341.1438.



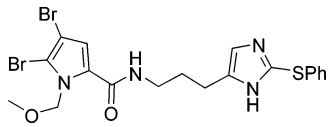
4-Bromo-1-methyl-1H-pyrrole-2-carboxylic Acid [3-(2-Phenylsulfanyl-3H-imidazol-4-yl)propyl]amide (37f). Following General Procedure C (Supporting Information), amide **36f** (0.149 g, 0.283 mmol) in 3 mL of THF was heated to reflux and treated with 0.750 mL of a 1.5 M HCl solution to give 0.067 g (56%) of the deprotection product **37f** as a colorless oil: IR (thin film) 3119, 1633 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.21−7.13 (m, 5H), 6.86 (br s, 1H), 6.82 (s, 1H), 6.65 (d, J = 1.5 Hz, 1H), 6.60 (d, J = 1.4 Hz, 1H), 3.82 (s, 3H), 3.38 (q, J = 6.1 Hz, 2H), 2.63 (t, J = 6.5 Hz, 2H), 1.82 (quint, J = 6.1 Hz, 2H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 161.2, 137.0, 136.1, 131.8, 130.8, 130.2, 130.0, 127.7, 126.7, 119.4, 114.3, 93.7, 38.1, 36.9, 28.3, 22.3; LRMS (ESI) m/z (relative intensity) 419.0 (100% M + H^+); HRMS (ESI) m/z calcd for $[C_{18}H_{20}BrN_4OS]^+$, 419.0541; found, 419.0562.



4,5-Dibromo-1-methyl-1H-pyrrole-2-carboxylic Acid [3-(2-Phenylsulfanyl-3H-imidazol-4-yl)propyl]amide (37i). Following General Procedure C (Supporting Information), amide **36i** (0.150 g, 0.248 mmol) in 3 mL of THF was heated to reflux and treated with 0.660 mL of a 1.5 M HCl solution to give 0.073 g (63%) of the deprotection product **37i** as a colorless oil: IR (thin film) 3154, 1632 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20−7.11 (m, 5H), 6.80 (s, 1H), 6.70 (s, 1H), 3.84 (s, 3H), 3.35 (q, J = 5.9 Hz, 2H), 2.62 (t, J = 6.4 Hz, 2H), 1.81 (quint, J = 6.2 Hz, 2H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 161.4, 137.2, 136.9, 132.5, 131.2, 130.6, 130.1, 128.5, 119.5, 115.1, 111.9, 98.1, 36.4, 36.4, 28.4, 22.7; LRMS (ESI) m/z (relative intensity) 496.9 (100% M + H^+); HRMS (ESI) m/z calcd for $[C_{18}H_{19}N_4OS\ Br_2]^+$, 496.9646; found, 496.9651.

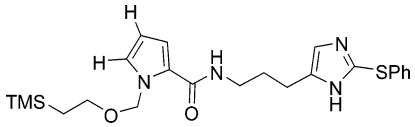


1-Methoxymethyl-1H-pyrrole-2-carboxylic Acid [3-(2-Phenylsulfanyl-3H-imidazol-4-yl)propyl]amide (37b). Following General Procedure C (Supporting Information), amide **36b** (0.300 g, 0.881 mmol) in 3 mL of THF was heated to reflux and treated with 2.35 mL of a 1.5 M HCl solution to give 0.213 g (71%) of the deprotection product **37b** as a colorless oil: IR (thin film) 3180, 1629 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.16−7.04 (m, 5H), 6.83 (t, J = 1.4 Hz, 1H), 6.76 (s, 1H), 6.69 (dd, J = 3.7, 1.5 Hz, 1H), 6.05 (dd, J = 3.7, 2.7 Hz, 1H), 5.52 (s, 2H), 3.43 (q, J = 6.0 Hz, 2H), 3.20 (s, 3H), 2.56 (t, J = 6.8 Hz, 2H), 1.76 (quint, J = 6.6 Hz, 2H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 162.7, 137.5, 136.7, 132.1, 131.0, 130.6, 130.2, 128.8, 126.0, 119.7, 115.1, 108.6, 78.6, 56.2, 38.6, 28.7, 22.7; LRMS (ESI) m/z (relative intensity) 371.1 (100% M + H^+); HRMS (ESI) m/z calcd for $[C_{19}H_{23}N_4O_2S]^+$, 371.1542; found, 371.1560.

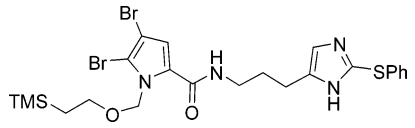


4,5-Dibromo-1-methoxymethyl-1H-pyrrole-2-carboxylic Acid [3-(2-Phenylsulfanyl-3H-imidazol-4-yl)propyl]amide (37g). Following General Procedure C (Supporting Information), amide **36g** (0.067 g, 0.11 mmol) in 3 mL of THF was heated to reflux and treated with 0.084 mL of a 1.5 M HCl solution to give 0.040 g (72%) of the deprotection product **37g** as a colorless oil: IR (thin film) 3180, 1629 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (br s, 1H), 7.21−7.13 (m, 5H), 6.83 (s, 1H), 6.81 (br s, 1H), 5.70 (s, 2H), 3.37 (q, J = 5.8 Hz, 2H), 3.27 (s, 3H), 2.62 (t, J = 6.2 Hz, 2H), 1.82 (quint, J = 5.9 Hz, 2H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 160.8, 137.1, 136.7, 132.2, 131.1, 130.4, 130.1, 129.1, 119.5, 116.1, 111.6, 99.9, 77.0, 56.4, 38.6, 28.3, 22.5; LRMS (ESI) m/z

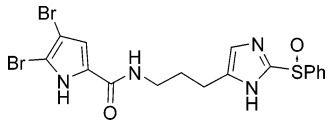
(relative intensity) 527.0 (100% M + H^+); HRMS (ESI) *m*/*z* calcd for $[C_{19}H_{21}Br_2N_4O_2S]^+$, 526.9752; found, 526.9766.



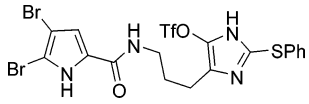
1-(2-Trimethylsilanylethoxymethyl)-1H-pyrrole-2-carboxylic Acid [3-(2-Phenylsulfanyl-3H-imidazol-4-yl)propyl]amide (37c). Following General Procedure C (Supporting Information), amide **36c** (0.315 g, 0.559 mmol) in 3 mL of THF was heated to reflux and treated with 1.49 mL of a 1.5 M HCl solution to give 0.224 g (88%) of the deprotection product **37c** as a colorless oil: IR (thin film) 3182, 1634 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14−7.06 (m, 5H), 6.85 (br d, J = 3.2 Hz, 1H), 6.77 (s, 1H), 6.68 (dd, J = 3.7, 1.6 Hz, 1H), 6.07 (t, J = 3.6 Hz, 1H), 5.58 (s, 2H), 3.49 (t, J = 8.6 Hz, 2H), 3.32 (q, J = 6.1 Hz, 2H), 2.58 (t, J = 6.2 Hz, 2H), 1.78 (quint, J = 6.5 Hz, 2H), 0.84 (t, J = 8.6 Hz, 2H), −0.08 (s, 9H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 162.8, 137.2, 136.8, 132.5, 131.1, 130.5, 130.0, 128.5, 126.2, 119.4, 114.8, 108.6, 76.7, 65.8, 38.4, 28.8, 22.5, 18.0, −0.8; LRMS (ESI) *m*/*z* (relative intensity) 457.2 (100% M + H^+); HRMS (ESI) *m*/*z* calcd for $[C_{23}H_{33}N_4O_2SSi]^+$, 457.2094; found, 457.2106.



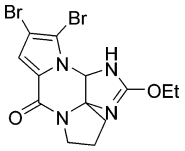
4,5-Dibromo-1-(2-trimethylsilanylethoxymethyl)-1H-pyrrole-2-carboxylic Acid [3-(2-Phenylsulfanyl-3H-imidazol-4-yl)propyl]-amide (37h). Following General Procedure C (Supporting Information), amide **36h** (0.243 g, 0.367 mmol) in 3 mL of THF was heated to reflux and treated with 0.979 mL of a 1.5 M HCl solution to give 0.187 g (83%) of the deprotection product **37h** as a colorless oil: IR (thin film) 3143, 1634 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (br s, 1H), 7.19−7.09 (m, 5H), 6.81 (s, 1H), 6.79 (s, 1H), 5.70 (s, 2H), 3.49 (t, J = 8.5 Hz, 2H), 3.32 (q, J = 5.8 Hz, 2H), 2.60 (t, J = 6.4 Hz, 2H), 1.81 (quint, J = 6.2 Hz, 2H), 0.85 (t, J = 8.5 Hz, 2H), −0.07 (s, 9H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 161.0, 137.1, 136.8, 132.5, 131.1, 130.5, 130.0, 129.1, 119.5, 116.1, 111.5, 99.8, 75.3, 66.2, 38.7, 28.5, 22.5, 18.0, −0.8; LRMS (ESI) *m*/*z* (relative intensity) 613.0 (100% M + H^+); HRMS (ESI) *m*/*z* calcd for $[C_{23}H_{31}Br_2N_4O_2SSi]^+$, 613.0303; found, 613.0327



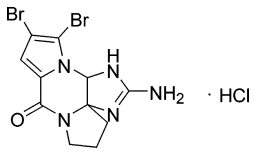
4,5-Dibromo-1H-pyrrole-2-carboxylic Acid [3-(2-Benzenesulfinyl-3H-imidazol-4-yl)propyl]amide (24b). Following General Procedure C (Supporting Information), 4,5-dibromo-1H-pyrrole-2-carboxylic acid [3-(2-benzenesulfinyl-3-dimethylsulfamoyl-3H-imidazol-4-yl)propyl]amide (0.500 g, 0.823 mmol) in 4 mL of THF was heated to reflux and treated with 2.20 mL of a 1.5 M HCl solution to give 0.186 g (45%) of the deprotection product **24b** as a white solid: mp 200−202 °C (dec); IR (thin film) 3043, 1629 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 80 °C) δ 7.79−7.76 (m, 2H), 7.61−7.59 (m, 3H), 7.31 (s, 1H), 6.86 (s, 1H), 3.20 (t, J = 6.7 Hz, 2H), 2.63 (t, J = 7.4 Hz, 2H), 1.78 (quint, J = 6.9 Hz, 2H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 159.6, 146.0, 141.2, 137.8, 133.4, 130.6, 128.4, 125.6, 120.2, 113.5, 105.0, 98.5, 38.2, 28.5, 22.6; LRMS (ESI) *m*/*z* (relative intensity) 498.9 (70% M + H^+); HRMS (ESI) *m*/*z* calcd for $[C_{17}H_{17}Br_2N_4O_2S]^+$, 498.9431; found, 494.9435.



Trifluoromethanesulfonic Acid 5-{3-[(4,5-Dibromo-1H-pyrrole-2-carbonyl)amino]propyl}-2-phenylsulfanyl-3H-imidazol-4-yl Ester (27). A stirring solution of amidosulfoxide **24b** (0.092 g, 0.18 mmol) in 3.5 mL of CH_2Cl_2 was cooled to −78 °C and treated with *i*-Pr_2NEt (61 μL, 0.37 mmol). After 5 min, Tf_2O (169 μL, 0.552 mmol) was added, and the reaction solution changed from colorless to red. The reaction mixture was held at −78 °C for 30 min and was then warmed to room temperature over 10 min and poured into H_2O (5 mL). The resulting solution was partitioned between CH_2Cl_2 and H_2O, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic fractions were dried with Na_2SO_4 and concentrated to give a yellow oil. Purification of this oil by flash column chromatography (1:1 EtOAc/hexanes) gave 0.010 g (9%) of the triflate **27** as an unstable yellow oil: IR (thin film) 3129, 1618 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 13.3 (br s, 1H), 12.7 (br s, 1H), 8.16 (t, J = 5.6 Hz, 1H), 7.37−7.15 (m, 5H), 6.89 (d, J = 2.4 Hz, 1H), 3.20 (q, J = 6.5 Hz, 2H), 2.58 (t, J = 7.4 Hz, 2H), 1.78 (quint, J = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.9, 140.6, 134.4, 130.4, 129.5, 128.1, 127.6, 127.0, 122.8, 112.4, 104.5, 97.7, 37.9, 28.3, 20.2; LRMS (ESI) *m*/*z* (relative intensity) 630.8 (100% M + H^+); HRMS (ESI) *m*/*z* calcd for $[C_{18}H_{16}N_4O_4F_3S_2Br_2]^+$, 630.8967; found, 630.8932. Carbon−fluorine coupling was not observed due to a paucity of material and the instability of **27**, which experienced decomposition even after short NMR acquisition times.



Ethylated Isourea (33). A stirring solution of dibromophakellstatin **1** (0.107 g, 0.274 mmol) in 10 mL of CH_2Cl_2 was treated with $NaHCO_3$ (0.460 g, 5.48 mmol). After 5 min, $Et_3O^+BF_4^-$ (0.260 g, 1.37 mmol) was added, and the reaction mixture was held at room temperature for 2 h and then poured into 10 mL of ice-cold aqueous $NaHCO_3$. The resulting solution was partitioned between CH_2Cl_2 and H_2O, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic fractions were dried with Na_2SO_4 and concentrated to give a yellow oil. Purification of this oil by flash column chromatography (alumina, gradient 70−100% EtOAc/hexanes) gave 0.051 g (45%) of the ethyl derivative **33** as a white solid: mp 208−210 °C (dec); IR (thin film) 3230, 1621 cm^{-1}; ^1H NMR (360 MHz, d_4-MeOH) δ 6.89 (s, 1H), 5.88 (s, 1H), 4.27−4.13 (m, 2H), 3.79 (br m, 1H), 3.69−3.61 (m, 1H), 2.25−2.07 (m, 4H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 154.8, 125.8, 114.9, 104.0, 102.4, 88.2, 72.5, 65.8, 44.2, 40.7, 20.2, 14.2; LRMS (ESI) *m*/*z* (relative intensity) 438.9 (100% M + Na^+); HRMS (ESI) *m*/*z* calcd for $[C_{13}H_{14}N_4O_2Br_2Na]^+$, 438.9381; found, 438.9405.



Dibromophakellin Hydrochloride (2a)•HCl. A neat mixture of isourea **33** (0.020 g, 0.048 mmol) and $EtCO_2^-NH_4^+$ (1.0 g, 11 mmol) was heated to 135 °C and held at this temperature for 30 min. The resulting dark-yellow solution was allowed to cool to room temperature, and the excess propionate salt was removed by

sublimation under vacuum at 80 °C to leave a brown oil. Purification of this oil by gravity column chromatography (Sephadex G-10, H_2O then MeOH) gave a white gum that was dissolved in 100 mL of CH_2Cl_2, and HCl (g) was bubbled through the solution for 10 min. The reaction mixture was then concentrated to give 0.012 g (59%) of dibromophakellin hydrochloride (**2a**)•HCl as a white solid: mp 218−220 °C (dec); IR (thin film) 3411, 1679, 1637 cm^{-1}; ^1H NMR (360 MHz, d_4-MeOH) δ 7.01 (s, 1H), 6.24 (s, 1H), 3.83 (ddd, J = 11.7, 8.4, 3.3 Hz, 1H), 3.68−3.60 (m, 1H), 2.46−2.42 (m, 2H), 2.25−2.13 (m, 2H); ^{13}C NMR (75 MHz, d_4-MeOH) δ 158.0, 156.5, 126.0, 117.1, 107.7, 104.1, 84.2, 70.2, 46.2, 40.1, 20.5; LRMS (ESI) m/z (relative intensity) 387.9 (70% M^+); HRMS (ESI) m/z calcd for $[C_{11}H_{12}N_5OBr_2]^+$, 387.9409; found, 387.9392.

Acknowledgment. Funding from the National Science Foundation (CHE 04-14877) is gratefully acknowledged.

Supporting Information Available: General experimental procedures; copies of ^1H NMR and ^{13}C NMR spectra for **2a**, **22b**, **24b**, **27**, **33**, **34**, **35c, 35g**, **35h**, **36a**−**i**, **37a**−**i,** 5-(3-Aminopropyl)-2-benzenesulfinylimidazole-1-sulfonic acid dimethylamide, 4,5-dibromo-1H-pyrrole-2-carboxylic acid [3-(3-dimethylsulfamoyl-2-phenylsulfanyl-3H-imidazol-4-yl)propyl]amide, and 4,5-dibromo-1H-pyrrole-2-carboxylic acid [3-(2-benzenesulfinyl-3-dimethylsulfamoyl-3H-imidazol-4-yl)propyl]amide. This material is available free of charge via the Internet at http://pubs.acs.org.

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